UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/523,803	09/20/2006	Kazuo Sakai	50680-002001	5350

21559 7590 04/11/2017

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
PRYOR, ALTON NATHANIEL

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
04/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KAZUO SAKAI, JOHN IENI,
and RAYMOND PRATT

Appeal 2014-008172
Application 11/523,803
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a method for treating major depression. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"'Depression (or depressive state)' is classified as a mood disorder and is the most common mental disease" (Spec. 1:16–17). "'Depression' . . . is classified as '296. xx: major depressive disorders' and 'minor depressive disorders" (Spec. 8: 4–5). "The major depressive disorders are further

---

[1] Appellants identify the Real Party in Interest as Eisai R&D Management Co., Ltd. (*see* App. Br. 2).

classified as 'single episode' which is a major depressive episode for the first time (single) and 'recurrent episode' which is experiences of two or more major depressive episodes in the past" (Spec. 8:4–10).

"[I]t has been unexpectedly discovered that when a cholinesterase inhibitor is combined with a selective serotonin reuptake inhibitor, milnacipran, or duloxetine, it is possible to treat depression, in particular refractory depression" (Spec. 4:24 to 5:2).

The Claims

Claims 1, 3–7, 12, 13, 19, 20, 31, 33, and 34 are on appeal. Independent claim 1 is representative and reads as follows:

> 1. A method for treating major depression in a patient in need thereof comprising administering donepezil or a pharmaceutically acceptable salt thereof, and (i) a selective serotonin reuptake inhibitor, (ii) milnacipran, an enantiomer thereof, a diastereomer thereof, a pharmaceutically acceptable salt thereof, an enantiomer of a pharmaceutically acceptable salt thereof, a diastereomer of a pharmaceutically acceptable salt thereof, an active metabolite thereof, or a prodrug thereof; or (iii) duloxetine, an enantiomer thereof, a pharmaceutically acceptable salt thereof, an enantiomer of a pharmaceutically acceptable salt thereof, an active metabolite thereof, or a prodrug thereof.

The Issue

The Examiner rejected claims 1, 3–7, 12, 13, 19, 20, 31, 33, and 34 under 35 U.S.C. § 103(a) as obvious Nagy,[2] Yoshimura,[3] Schrag,[4] Burt,[5] Kemmerich,[6] and Perlis[7] (Ans. 2–5).

The Examiner finds Nagy teaches "Sertraline HCl, a selective serotonin re-uptake inhibitor, can be used in the treatment of depressive symptoms in elderly patients including those with [Alzheimer's disease ("AD")] and "tests to determine drug-drug interaction in the co-administration of donepezil HC1 and sertraline" (Ans. 3). The Examiner finds Yoshimura teaches "paroxetine and donepezil are co-administered to a patient with depressive pseudodementia" and Schrag teaches "with respect to a patient with Parkinson's disease donepezil is effective in treating cognitive function and behavioural disorder; and with respect to depressive symptoms a selective serotonin re-uptake inhibitor is effective" (*id.*). The

---

[2] Nagy et al., *Concurrent administration of donepezil HCI and sertraline HCI in healthy volunteers: assessment of pharmacokinetic changes and safety following single and multiple oral doses*, 58 BR. J. CLINICAL PHARMACOLOGY 25–33 (2004).
[3] Yoshimura et al., *A case of paroxetine having significant effect on depressive pseudodementia*, 22 PHARMA MEDICA 134–136 (2004) (We rely upon the English translation, numbered sequentially from the first page).
[4] Schrag, A., *Psychiatric aspects of Parkinson's disease*, 251 J. NEUROL. 795–804 (2004).
[5] Burt, T., *Donepezil and Related Cholinesterase Inhibitors as Mood and Behavioral Controlling Agents*, 2 CURR. PSYCHIATRY REP. 473–478 (2000).
[6] Kemmerich et al., *Donepezil in therapy-refractory depression*, 10 EUROPEAN NEUROPSYCHOPHARMACOLOGY S264 (2000).
[7] Perlis et al., *The Effects of an Orally Administered Cholinergic Agonist on REM Sleep in Major Depression*, 51 BIOL. PSYCHIATRY 457–62 (2002).

Examiner finds Burt teaches "donepezil has an effect of improving depression in a patient with Alzheimer Disease"; Kemmerich teaches "donepezil is effective in treating refractory depression in a patient who does not suffer from Alzheimer Disease"; and Perlis teaches "donepezil HCl is effective for a patient with major depression" (Ans. 4).

The Examiner finds it obvious to "coadminister paroxetine and donepezil to treat all types on depressing since the prior art teaches that donepezil individually and paroxetine individually can be used to treat depression" (Ans. 5).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the prior art renders the claims obvious?

Findings of Fact

1. Nagy teaches:

> There is a high incidence of co-morbid depression in patients with AD, and accumulating evidence shows that this can have profound effects on both the long-term functioning of AD patients and the wellbeing of their caregivers. . . . Sertraline HCl - a selective serotonin re-uptake inhibitor (SSRI) - is indicated for the treatment of depression and anxiety disorders.

(Nagy 26, col. 1–2).

2. Nagy teaches: "Donepezil HCl is a potent and specific piperidine-based inhibitor of acetylcholinesterase (AChE), and has been demonstrated in placebo-controlled trials to significantly improve cognition" (Nagy 26, col. 1).

3. Nagy teaches the "concurrent administration of donepezil HCl and sertraline HCl was well tolerated, with no serious AEs reported during this study. This observation is consistent with clinical data from AD patients who received both donepezil HCl and sertraline HCl" (Nagy 32, col. 1).

4. Yoshimura teaches a patient "was diagnosed as having Alzheimer's disease" (Yoshimura 2) and "[a]ccording to the diagnosis, administration of 3 mg/day of donepezil was started . . . From the day she visited us, administration of paroxetine 20 mg (once after supper) was initiated" (Yoshimura 3).

5. Yoshimura teaches "paroxetine could be the first choice drug for depressive state in aged persons" (Yoshimura 5).

6. Schrag teaches "[o]pen label trials have reported that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, citalopram, paroxetine or fluvoxamine are effective in treating depression in PD [Parkinson's disease] with only rare deterioration of parkinsonism" (Schrag 797, col. 1).

7. Burt teaches in "a retrospective study in 86 AD [Alzheimer's disease] patients Mega *et al.* observed significant improvements from baseline in delusions, agitation, anxiety, disinhibition, and irritability in responders to donepezil" (Burt 475, col. 1).

8. Kemmerich teaches "[d]onepezil was administered to two female patients (Pl, P2), 67 and 64 years old respectively, diagnosed with severe therapy-resistant depression (ICD-10 F32.3 (P1), F33.3 (P2))" (Kemmerich S264, col. 1).

9. Kemmerich teaches: "In both patients, we observed an antidepressant effect accompanied by cognitive improvement after administration of donepezil" (Kemmerich S264, col. 1).

10. Perlis teaches: "We have evaluated donepezil 10 mg (Aricept, Pfizer-Eisai) to determine whether a single 10-mg dose alters REM timing and whether this effect occurs preferentially in patients with MDD [major depressive disorder]" (Persis 458, col. 1).

11. Perlis teaches "both of the orally active drugs, donepezil and RS 86, induce REM sleep more quickly in depressed patients than in healthy control subjects" (Perlis 460, col. 2).

12. The Specification teaches: "In accordance with ICD-10, 'depression' is classified and diagnosed as follows. F 32: Depressive episode. In the three types of typical depressive episodes (light (F 32.30), medium (F 32.1) or severe (F 32.2 and F 32.3), patients are usually bothered by depressive mood" (Spec. 11:8–11).

Principles of Law

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Ans. 2–5; FF 1–11) and agree that claim 1 would have been obvious to a person of ordinary skill in the art. We address Appellants' arguments below.

> Appellants contend
>
> > a skilled artisan, reading the Perlis reference, which is the only cited reference that mentions major depression, would not be motivated to use donepezil to treat major depression, and thus to co-administer donepezil and a previously known antidepressant for treatment of major depression. As to the other cited references, the Applicant reiterates that they do not even mention major depression.

(App. Br. 5; underlining omitted). Appellants contend "Kemmerich is cited for teaching that donepezil is effective for treating refractory depression. However, as discussed at length in the Applicant's prior replies, Kemmerich does not teach that donepezil, by itself, has antidepressant activity. Further, Kemmerich does not mention major depression" (*Id.* at 6).

We do not find these arguments persuasive.[8] Kemmerich specifically teaches treatment of "severe therapy-resistant depression" with donepezil (FF 8) and uses the same ICD-10 codes, F32.3 and F33.3, as the Specification (FF 12). Thus, we agree with the Examiner that "Kemmerich treats refractory depression which is a form of major depression" and that "Appellants have not shown that the depression types differ" (Ans. 11). That is, the evidence of record supports the Examiner's position that when Kemmerich refers to "severe therapy-resistant depression", that condition is a type of "major depression" within the scope of claim 1. Appellants provide no evidence persuasively rebutting the position of the Examiner.

Nagy evidences that SSRIs and sertraline in particular, are useful for treatment of depression (FF 1). Nagy also evidences that donepezil and sertraline may be safely coadministered (FF 3), supporting the Examiner's reasonable expectation of success. The use of the combination of donepezil and sertraline to treat depression (FF 1, 3, 8) is nothing "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

Appellants address the Perlis reference, which also evidences that donepezil may be safely administered to patients with major depression (FF 10), and contend "Perlis **teaches away** from using donepezil to treat major depression" (App. Br. 3).

---

[8] In affirming a multiple reference rejection under 35 U.S.C. § 103, the Board may rely on fewer than all of the references relied on by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961).

Although we need not rely on Perlis for the obviousness of claim 1 because we find Kemmerich and Nagy sufficient, we also find Appellants' "teaching away" argument unpersuasive. "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed". *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Appellants do not identify, and we do not find, any teaching in Perlis that discourages, discredits or otherwise criticizes the use of donepezil for treatment of major depression. We recognize that the REM latency of patients with MDD changes (*see* Perlis 459, table 2), but that result has a significance value of 0.06, which does not meet the threshold of 0.05 for statistical significance.

Moreover, Perlis provides no direct evidence regarding the effect of donepezil on symptoms of patients with major depression while Kemmerich specifically teaches "we observed an antidepressant effect accompanied by cognitive improvement after administration of donepezil" (FF 9).

> Where the prior art contains "apparently conflicting" teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered "for its power to suggest solutions to an artisan of ordinary skill. . . . considering the degree to which one reference might accurately discredit another."

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006). Kemmerich provides a direct teaching of benefit of donepezil for patients with severe depression (FF 8–9) while Perlis provides indirect teachings regarding nonsignificant effects of donepezil on the REM movements of

patients with depression (FF 10–11). As we balance these conflicting teachings, we find Kemmerich more persuasive regarding the expected effects of donepezil on patients with major depression than Appellants' interpretation of Perlis.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the prior art renders the claims obvious.

SUMMARY

In summary, we affirm the rejection of claim 1, under 35 U.S.C. § 103(a) as obvious Nagy, Yoshimura, Schrag, Burt, Kemmerich, and Perlis. Claims 3–7, 12, 13, 19, 20, 31, 33, and 34 fall with claim 1.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED